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PERSPECTIVES

Baa, Baa, black sheep, are your kidneys full?

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The effect of genetic variance on blood pressure is about 50 %. Thus, environmental influences are major. Recent evidence has suggested that environment very early in life may influence blood pressure decades later. Barker and co-workers first proposed that intrauterine malnutrition, marked by low birth weight, predisposes persons to type 2 diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease (Barker & Martyn, 1992; Barker *et al.* 1993). In this issue of *The Journal of Physiology* Wintour and colleagues observed that if pregnant sheep receive corticosteroids at days 26–28 during their gestation of 150 days, their offspring develop hypertension as adults (Dodic *et al.* 2002). Brenner & Chertow (1994) have suggested that reduction in the number of nephrons at birth leads to hyperperfusion of each nephron and resulting glomerular sclerosis, further nephron death, and a cycle of increasing blood pressure and nephron death. Glomerular filtration rate need not be reduced in this model, since the remaining (or the fewer) glomeruli do more filtration work and presumably increase in size. In rats, a decrease in nephron number of about 30 % was reported if the mothers received corticosteroids at days 11–16 of their 3-week pregnancy (Ortiz *et al.* 2001). A similar phenomenon has been described in rats that were food-restricted during pregnancy (Regina *et al.* 2001). Wintour *et al.* (2003) now report that dexamethasone treatment of pregnant ewes results in an increase in blood pressure of about a 10 mmHg in their offspring at 7 years of age and that their glomerular number is reduced about 40 %. The glomeruli in the dexamethasone offspring were larger and the proximal tubules were dilated, perhaps reflecting more filtrate per nephron.

The story seems consistent. Recently, Keller *et al.* (2003) reported that hypertensive German autoaccident victims had fewer glomeruli, compared to nonhypertensive German autoaccident victims. The reduction was similar to that reported by Wintour *et al.* (2003) in their sheep. The hypertensive humans with their fewer glomeruli also featured larger glomeruli. Another consistency is the relatively modest glomerular sclerosis observed in the hypertensive humans. Wintour *et al.* (2003) also found no difference in the severity of glomerulosclerosis in the sheep. Some sclerosis might be expected since the hyperfiltering glomeruli may be working themselves to death. Indeed, later in the process, sclerosis may occur.

Are there weaknesses in these studies or can we accept the explanations offered? Clearly, a careful look at methodology is warranted. Human kidneys are said to contain about a million glomeruli so counting them is probably not trivial. Observers, particularly clinicians such as yours truly, are intimidated by methods that they really do not understand. Wintour *et al.* (2003) perfused the right kidneys with paraformaldehyde. One half was taken for sampling. Slices were made and every third 5 mm slice was chosen at random. The slices were cut into strips of 5 mm in width, then smaller blocks were made and every 15th block was sampled. The glomeruli were then estimated with help of physical dissectors. In the human study, samples were subjected to a three-dimensional 'fractionater' method, also something above-and-beyond the average clinician (Keller *et al.* 2003). Perhaps both methods are entirely reliable, but in terms of both studies, a second totally independent method to verify the first would inspire confidence. For instance, casts could be made of the renal vasculature with methacrylate, the tissues could be removed by digestion and then the tufts examined for glomerular number.

If we accept these publications at face value, explaining the hypertension is also not necessarily easy. Wintour *et al.* (2003) point out that uninephrectomy after birth does not necessarily increase blood pressure. The authors implicate additional mechanisms including up-regulation of angiotensinogen and angiotensin II receptors (Moritz *et al.* 2002). Increased sodium channel expression, perhaps promoting salt sensitivity, has also been suggested as an explanation for imprinting (Manning *et al.* 2002).

'Perinatal programming' is the buzz phrase applied to the notion that events during gestation can have far-reaching effects into adulthood. Clearly, this model is a pristine example. Mutations or variations in genes controlling and influencing renal development, such as *PAX* genes, *WNT* genes, or the renin–angiotensin system genes could influence nephron number and explain genetic variance of blood pressure (Ingelfinger, 2003). Children with unilateral renal agenesis were found to have higher blood pressures than children losing one kidney shortly after birth (Mei-Zahav *et al.* 2001). A host of environmental factors in addition to dexamethasone might also influence renal development. These include medications ingested during pregnancy, nutritional factors as espoused by the Barker hypothesis, or maternal disease such as preeclampsia.

Wintour *et al.* (2003) have not addressed the clinical question of what happens to the offspring of mothers ingesting corticosteroids during pregnancy. Reports indicating that offspring of transplant patients, mothers with Lupus erythematosus, asthma, and similar conditions should indicate the presence of hypertension in the offspring. Perhaps no-one has looked carefully. Here are important clinical questions to be answered. All the more compelling reason that these fascinating animal data and the recent human study be verified as soon as possible.

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